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A systematic review of neurological manifestations of SARS-CoV-2 infection: the devil is hidden in the details

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Ethical approval

Not required.

Abstract

Background

We systematically reviewed available evidence for reports of neurological signs and symptoms in Coronavirus disease (COVID)-19 patients to identify cases with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection or immune-mediated reaction in the nervous system.

Methods

We followed PRISMA guidelines and used the MEDLINE, EMBASE, Google Scholar, MedRxiv and ChinaXiv databases to search for papers on COVID-19 and nervous system involvement which were published from January 1st to April 24th 2020. Data on design, sample size, neurologic assessment and related work-up were extracted. Biases were assessed with the Newcastle-Ottawa scale.

Results

We analysed 27 publications on potential neuroinvasive or parainfectious neurological complications of COVID-19. The reports focused on smell and taste (n=5) and evaluation of neurological symptoms and signs in cohorts (n=5). There were cases of Guillain-Barré syndrome/Miller-Fisher syndrome/cranial neuropathy (7 cases), meningitis/encephalitis (9 cases) and various other conditions (5 cases). Patients with cerebrospinal fluid (CSF) examination and in particular SARS-CoV-2 PCR was negligible. Amongst, two had a positive SARS-CoV-2 PCR exam of CSF specimen. The study of potential parenchymal involvement with magnetic resonance imaging was rare. Only 4 reports received a rating for the highest quality standards.

Conclusion

This systematic review failed to establish comprehensive insights to nervous system manifestations of COVID-19 beyond immune-mediated complications as aftermath of respiratory symptoms. The authors therefore provide guidance for more careful clinical, diagnostic and epidemiological studies to characterize the manifestations and burden of neurological disease caused by SARS-CoV-2 on behalf of the Infectious Disease Panel of the European Academy of Neurology.

Keywords

COVID-19; SARS-CoV-2; neurological complications; neuroinvasion; cerebrospinal fluid; encephalitis

Introduction

The clinical spectrum of SARS-CoV-2 infection is wide, and encompasses asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and sometimes death. From a neurobiological and translational viewpoint, neurological manifestations can be expected in COVID-19. This is substantiated on the one hand by a few cases with neurologic signs and symptoms and detectable virus load in cerebrospinal fluid (CSF) during the SARS-CoV-1 epidemic in 2003 [1]. SARS-CoV-1 and SARS-CoV-2 share genetic sequences but SARS-CoV-2 has a 10-20 times higher binding affinity to ACE2 [2]. On the other hand, angiotensin converting enzyme-2 (ACE-2), the functional receptor utilized by SARS-CoV-1 and -2 for cell entry, is not only expressed in the lungs but also in the central nervous system (CNS) [3, 4]. Expression of ACE-2 is found in neurons and non-neuronal cells, the latter include astrocytes, oligodendrocytes and olfactory support cells [5, 6]. Moreover, infection of neurons with SARS-CoV-1 has been proven in transgenic mice and several presumed routes of CNS entry were described in preclinical models [7]. In a report from Wuhan, China more than a third of the hospitalized COVID-19 patients had some sort of nervous system–related clinical signs or symptoms [8]. These included on the one hand more specific conditions such as loss of sense of smell or taste, myopathy, and stroke. There were non-specific symptoms such as headache, impaired level of consciousness, dizziness, or seizure on the other hand. From a neuroinfectiologic viewpoint, the relevance of these findings is limited; these conditions can be coincidental, secondary to systemic complications or a side-effect of therapy. Only further diagnostic details such as focused neuroimaging, evaluation cardiovascular risk factor and comorbidities, assessment of prothrombotic or systemic hyperinflammatory states, presence of intrathecal inflammation and systematic exclusion of differentials would enable a placement within the spectrum of COVID-19 complications.

This study therefore aimed to identify clinical cases of confirmed nervous system invasion or postinfectious neurological disease in the available COVID-19 literature on the basis of a systematic review. Hereupon, members of the Infectious Disease Panel of the European Academy of Neurology (EAN) compiled guidance for the diagnostic approach, which emphasizes the need for precise case definitions and standards for reporting.

Methods

A systematic review was carried out to study all cases reporting nervous system involvement in patients with proven SARS-CoV2 infection. The protocol followed the PRISMA guidance for reporting of systematic reviews. MEDLINE, EMBASE, Google Scholar, MedRxiv and ChinaXiv database were searched for papers

published from 1st January 2020 to April 24th 2020 regarding the nervous system and COVID-19. The search strings for PubMed were as follows: (("COVID"[All Fields] OR “coronavirus”[All Fields] OR “SARS-Cov-2”[All Fields]) AND (("neurology"[MeSH Terms] OR "neurolog*"[All Fields]) OR ("brain"[MeSH Terms] OR "brain"[All Fields]) OR ("neuro"[All Fields]) OR ("nervous system"[MeSH Terms] OR "nervous system"[All Fields])) AND ("2020/01/01"[PDAT] : "2020/04/24"[PDAT])). We also hand-searched reference lists of all articles identified in the electronic search using common search engines (e.g. google, bing).

The search selected studies reporting neurological features of patients with SARS-CoV-2 infection. Studies were identified after search and data were extracted regarding: study design, sample size, neurological assessment and diagnostic workup including brain imaging and CSF analysis. Biases were assessed with Newcastle-Ottawa scale [9].

Results

The systematic search yielded 102 papers, of which 30 were eligible for full-text assessment (Figure 1 for PRISMA flow-chart). Four were excluded; these were commentaries, response letters and review articles proposing on SARS-CoV-2 nervous system invasion but did not comprise clinical findings.

Twenty-six publications reporting neurological disturbances in patients with SARS-CoV-2 infection were evaluated, the major readouts are shown in Table 1. Bias assessment revealed low to fair quality more than half of the studies (14/27, 52%), as shown in Figure 2. This was mainly due to selection and reporting bias, as well as on the basis of uncertain exposure and lack of testing for SARS-CoV-2 with PCR in CSF. Only 4 reports reached a rating for high quality; one study evaluated neurological diagnoses of deceased patients with COVID-19 [10], another studied neurological signs and symptoms in a cohort of hospitalized COVID-19 patients [8], and a case series of peripheral nervous system dysfunction with in-depth phenotyping and diagnostic workup [11]. The fourth study described the clinical characteristics, laboratory features, treatment, and outcomes of cerebrovascular disease complicating SARS-CoV-2 infection [12]. Among the consecutively admitted 221 patients with COVID-19, 11 (5%) had acute ischemic stroke, 1 (0.5%) cerebral venous sinus thrombosis (CVST), and 1 (0.5%) cerebral hemorrhage.

Five observational studies evaluated smell and taste dysfunction. The first study used an internet-based platform in adults who underwent testing for COVID-19 and found a higher rate of smell and taste impairment in SARS-CoV-2 positive patients [13]. The second report was a European multicenter study of mild-to-moderate COVID-19 patients which used standardized questionnaires [14]. They found olfactory

and gustatory dysfunction in 85.6% and 88.0%, respectively. The third study used an online checklist inquired for self-reported anosmia/hyposmia [15]. In that cohort, 48% had hyposmia or anosmia and the onset was reported as sudden in 76%. The fourth report was a case-control study of smell and taste disorders among patients positive for SARS-CoV-2 on nasopharyngeal swab examination and also included SARS-CoV-2 negative patients as controls [16]. They found that COVID-19 patients were significantly younger (81%) and a high rate of smell (45%) and taste disorders (90.%). The fifth study smell dysfunction in 98% of the SARS-CoV-2 nasopharyngeal swab PCR positive patients and reported that this was evident for all 40 odorants studied [17]. The study also had a age- and sex-matched control group. None of these five studies provided data CSF analysis or brain imaging.

Five studies examined neurological disorders in cohorts. In the first study, hypoxic encephalopathy was the cause of death in 20% of patient who died from COVID-19 [10]. The second report assessed neurologic manifestations in a cohort hospitalized at three dedicated COVID-19 inpatient centers [8]. They found that 36.4% had various neurologic manifestations that involved the CNS, peripheral nervous system (PNS), and skeletal muscles. Brain imaging, CSF analysis and further workup were reported in neither of the studies. The third study reported neurologic features in 90.6% of consecutive patients admitted because of acute respiratory distress syndrome (ARDS) due to COVID-19 and treated at the ICU [18]. Confusion, agitation, pyramidal signs and dysexecutive syndrome were the most common clinical manifestations. Cerebral magnetic resonance imaging (MRI) was performed in 13/58 (22%), there was evidence for leptomeningeal enhancement in 62% and ischemic stroke in 23%. EEG (8/58, 14%) and CSF examinations were performed in some patients (7/58, 12%). None of the patients had a pleocytosis in CSF. A multicentre retrospective study evaluated the occurrence of seizures in COVID-19 patients [19]. There was not a single case of symptomatic seizures or status epilepsy among this cohort in which patients with epilepsy were excluded a priori. The fifth study has been already covered above and concerned the rate of acute cerebrovascular events (6%) in a cohort of COVID-19 patients [12]. The average of time from symptoms of SARS-CoV-2 infection to clinical manifestation of cerebrovascular disease was 10 days (interquartile range 1-29). The patients with cerebrovascular disease were significantly older, more likely to suffer from severe respiratory disease and more likely to have cardiovascular risk factors and medical history of cerebrovascular disease. They were also more likely to have an increased inflammatory response and hypercoagulable state.

Four publications reported eight cases of Guillain-Barre syndrome (GBS) in patients with confirmed SARS-CoV-2 infection. Nerve conduction studies disclosed both demyelinating and axonal neuropathies (n=4 and n=4, respectively). All but one case occurred with a time lag from the respiratory symptoms, the

range was 5 to 22 days. In the remaining case the clinical manifestation of GBS preceded COVID-19 symptoms by 8 days [20]. In the case series of five GBS patients, three patients had high protein levels and all tested negative for SARS-Cov-2 in CSF, as well as for anti-ganglioside antibodies [11]. The other reports did not perform PCR for SARS-CoV-2 or testing for immunoglobulin levels, and did not investigate antiganglioside antibodies in CSF or serum. In addition to the GBS cases, a case of Miller-Fisher syndrome with positive GD1b-IgG and a case of multiple cranial neuropathies, both with negative SARS-CoV-2 PCR in CSF, were found [21].

Nine cases of encephalitis/meningitis and presumed association with COVID-19 were reported in 8 publications. Amongst was a case of encephalitis in a patient with negative SARS-CoV-2 testing in both nasopharyngeal swab and CSF (normal cell count), no MRI was performed [22]. Another patient with presumed encephalitis had normal cell count and negative SARS-CoV-2 PCR in CSF, an MRI was not performed [23]. A similar constellation was reported for another case [24]. There is a patient with a diagnosis of COVID-19 related encephalitis for which data could only be retrieved from the hospital report [25]. In that case, the neurological symptoms included seizures and hiccups and SARS-CoV-2 PCR of CSF was positive. For the case of acute necrotizing encephalitis, a SARS-CoV-2 PCR was not performed in CSF [26]. A pathogenesis triggered by a COVID-19-related cytokine storm was subsequently assumed. A positive SARS-CoV-2 PCR in CSF was present in a patient with right temporal lobe encephalitis and ventriculitis [27]. Two patients were classified as meningo-encephalitis in association with COVID-19 [28]. Both had encephalitic symptoms, including non-convulsive status epilepticus and mental changes, with normal MRI and negative SARS-CoV-2 PCR in CSF. A case of meningoencephalitis was described, the patient had meningism, headache, fever and seizures, and was PCR was negative for SARS-CoV-2 in CSF [29].

There were 5 further case reports, which were related to various aspects. A patient in whom the authors assumed myelitis as final diagnosis [30]. In detail, the patient had a myelopathic syndrome 7 days after the onset of respiratory symptoms but was not evaluated with MRI nor lumbar puncture. There is a case of presumed acute disseminated encephalomyelitis (ADEM) with only minimal contrast-enhancement on brain MRI [31]. CSF examination was normal (cell count, protein, glucose), SARS-CoV-2 PCR was only performed for nasopharyngeal swab, which was positive. Furthermore, there is a patient with pre-existing epilepsy related to Herpes-simplex virus encephalitis who presented with non-convulsive status epilepticus in the context of COVID-19 infection [32]. The authors discuss fever as the cause of lowering the threshold for seizures in a brain with structural damage. The case of intracerebral hemorrhage which occurred 3 days after fever and respiratory symptoms did not have obvious coagulation disturbances [33].

Vascular imaging and CSF diagnostic were not performed. A patient with headache, altered mental status, fever, and cough was classified as acute encephalopathy [34]. EEG ruled out status epilepticus, CSF showed normal results and SARS-CoV-2 PCR in CSF was not done.

Overall, there were 2 patients positive for SARS-CoV-2 PCR of CSF among the 4 examined patients [25, 27].

Discussion

Our systematic search yielded only a limited number of studies and a significant reporting bias. This does not enable an in-depth characterization of neuroinfectious diseases associated with COVID-19. Indeed, quality, design and sample size of the available studies detains us from conclusion on possible direct neuroinvasive disease caused by SARS-CoV-2. The available literature does, however, provide evidence for unspecific symptoms commonly seen in viral infections including smell and taste disturbances, and the chance of immune-mediated peripheral nerve involvement. Our analysis also suggests that there is an overdiagnosis of neurological disorders due to the inappropriate use of case definitions and restricted exclusion of potential mimics.

Nervous system involvement has been reported during previous coronavirus epidemics. Interestingly, the analysis of the SARS-CoV-1 and MERS epidemic identified only a few anecdotal case reports and could not provide comprehensive insights to the clinical and radiological picture of neurological disease [1]. Moreover, there are preclinical studies reporting the neuroinvasive potential of coronaviruses and their immunogenicity [3]. The GBS we identified in our analysis are more consistent with a parainfectious disorder, i.e. a syndrome occurring during or soon after the viral syndrome, rather than a postinfectious syndrome. The limited literature for the COVID-19 outbreak could be seen in the restricted documentation due to the tying up of resources posed by the medical challenges. Indeed, it is conceivable that most emphasis was placed on the management of severe respiratory symptoms and restricted ICU capacity. It is obvious that neurologists are required for the care of COVID-19 patients [35, 36]. Their active involvement is not only mandatory for the work-up of presumed infectious and immune-mediated conditions but also for patients with reduced consciousness and nervous system complications of cardiac, pulmonary and coagulation disturbances related to SARS-CoV-2 [36]. Moreover, hypoxic brain injury may be the reason for clinical deterioration in a subgroup of patients. The potential association of SARS-CoV-2 with cerebrovascular diseases needs to be assessed in more detail; prospective trials with systematic use of ancillary investigations to confirm direct and indirect mechanism of action are mandatory in order to

gain further insights. From a neuroinfectiologic viewpoint, the major limitation of the available reports were that precise case definitions were not used, CSF testing was performed only in a subgroup of patients and exclusion of potential other diagnoses were reported only on occasion. There were just 2 cases with positive SARS-CoV-2 PCR in CSF among 27 patients with potential neurologic symptoms and proven COVID-19. However, to date nothing is known about the sensitivity of this detection method for the examination and CSF. Indeed, CSF examination for tick-borne encephalitis virus with PCR is not a standard due to a low sensitivity of the method and probably also transient presence of the virus in CSF. The best diagnostic approach to diagnose CNS infection with SARS-CoV-2 or parainfectious immune reaction associated with SARS-CoV-2 remains to be elucidated. Until now, no reports about intrathecal SARS-CoV-2-specific IgG synthesis in these cases is available but could be key for diagnosis. In addition, a better understanding of the reported non-specific symptoms including olfactory and gustatory disturbances, impaired consciousness and encephalopathy is needed. The systemic inflammatory response is a relevant feature of severe COVID-19 and could explain some of these scenarios.

The current analysis tells us that we do need more careful clinical, diagnostic and epidemiological studies to define the manifestations and burden of neurological disease caused by SARS-CoV-2. In this regard, we see a clear need for the use of precise case definitions and focused diagnostic work-up to distinguish non-specific complications of severe disease and focused reporting of neurological involvement in association with SARS-CoV-2 infection. Moreover, appropriate investigations are required to rule out other established causes of brain infections and parainfectious disease before attributing a condition to SARS-CoV-2. It also needs to kept in mind that SARS-CoV-2 causes a large number of asymptomatic or mildly symptomatic infections. A coincidental infection may exacerbate a so far asymptomatic or known neurological disease of other causes. Here, we provide guidance for assembling key clinical and paraclinical data which are required to establish insights to true spectrum of direct and indirect effects of SARS-CoV-2 infection on the nervous system (Table 2)::

1. The timing and results from nasopharyngeal swab PCR needs to be reported. Most important is the relation to the development of respiratory and neurological signs/symptoms. As soon as the antibody testing gets more widely available, this also pertains to this method. Both IgM and IgG need to be reported. For all detection methods, the testing kit and ideally the exact values need to be mentioned.
2. Potential differentials need to be ruled out: frequent mimics in a report from Spain of patients evaluated for SARS-CoV-2 infection included hypercapnia, renal or liver failure and side-effects of

drug therapy [37]. Comorbidities are frequent in certain patients and risk factors for neurological complications need to be identified.

3. If neuroinvasion or immune-mediated disease of the nervous system is suspected, it is mandatory to perform PCR testing for SARS-CoV-2 in CSF and anti-SARS-CoV-2 IgM/IgG testing in serum and CSF to check for intrathecal humoral immune reaction. It will be of major importance to determine whether PCR of CSF specimen is sensitive enough and define the time window of potential SARS-CoV-2 detection in relation to respiratory and neurological symptoms.
   The list of differential diagnoses for meningitis, encephalitis and myelitis is extensive [38, 39]. A guidance is shown in Table 2. We recently summarized potential indications for CSF examination [1]. Briefly, a permissive strategy for CSF testing should be exerted
   - on suspicion of encephalitis
   - new focal neurological deficit of no plausible differential etiology/no better explanation
   - delirious condition of no plausible differential etiology or no better explanation
   - acute cerebrovascular disorders
   - convulsive or non-convulsive seizures of no plausible differential etiology or no better explanation and
   - ICU patients with disorders of consciousness of no plausible differential etiology or no better explanation.

   The distinction of encephalopathy and encephalitis needs to be done according to standard criteria [40]. Brain MRI is critical and contrast-enhanced sequences are mandatory [41]. Coagulation disorders are relatively frequently encountered among COVID-19 patients and need to be considered in the workup of cerebrovascular disorders [42, 43]. In cases of peripheral nervous system involvement nerve conduction studies and electromyographic findings need to be reported, and antibodies to specific for immune-mediated conditions to provide differentials with critical illness neuropathy, acute non-inflammatory neuropathies and myopathy [44].

4. Reporting of timing and type of treatment. There is currently no study evidence for efficacy of a specific treatment for SARS-CoV-2 [45]. Guideline for the management of respiratory symptoms and systemic complications are outlined elsewhere, many be regionally distinct and are likely to be updated on a regular basis. With regard to neuroinfectious manifestations, one should be adhere to guidance on the management of viral meningitis and encephalomyelitis [46]. The management of immune-mediated conditions including GBS and Miller-Fisher syndrome should follow standard guidelines, with intravenous immunoglobulin (IVIG) or plasma exchange as first-

line options [44]. Coagulation disorders and other systemic complications of SARS-CoV-2 are likely to be of relevance for neurological care and complications. While an increased risk of seizures has not been reported so far, the potential interaction of antiepileptics and antiviral/-microbial therapy need to be kept in mind.

5. We do need information on critical care illness, prognostic factors and outcome.
6. The neuropathological evaluation of patients who died from SARS-CoV2 infection and had neurological symptoms or atypical clinical courses could provide invaluable insights,

Conclusion

Appropriate data collection, use of precise case definitions and concerted action for larger clinical studies are required to establish a better understanding of neuroinvasive and immune-mediated conditions in the context of SARS-CoV-2 infection. This is not only critical for improved diagnosis and management but also for the development of specific therapies in clinical treatment trials. We therefore propose a reassessment of the available literature on neurological complications in 3-6 months on the basis of a follow-up analysis. It would be interesting to evaluate whether a change in the quality of the reports took place in the meantime.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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Figures

Figure 1 PRISMA flow-chart

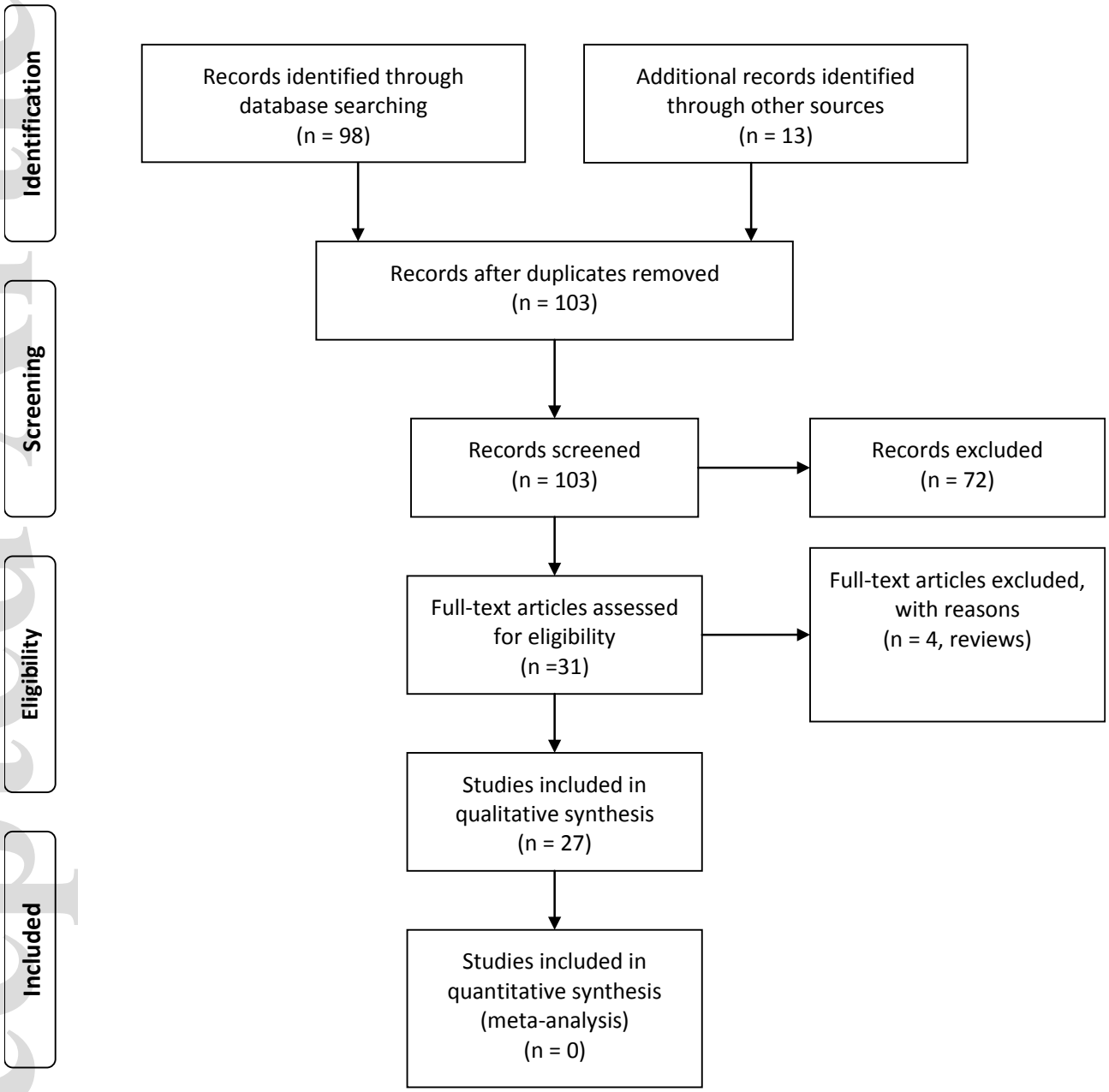

Figure 2 Assessment of study bias using the Ottawa-Newcastle scale

	Risk of bias									
	Selection					**Outcome**				
Author	Representativeness of the exposed cohort	Selection of the cohort/sample	Ascertainment of exposure Demonstration that outcome of interest was not present at start of study		**Comparability**	Assessment of outcome	Follow-up	Adequacy of follow up of cohorts	**Overall**	**Overall quality**
Bagheri (2020) [1]	1	1	1	0	1	0	1	1	6	moderate
Beltran-Corbellini (2020) [2]	1	1	1	0	1	0	1	1	6	moderate
Bernard-Valnet (2020) [3]	0	1	1	1	0	1	1	1	6*	moderate
Chen (2020)[4]	1	1	1	1	2	1	1	1	9	high
Duong (2020)[5]	0	0	0	1	0	1	1	1	4	low
Filatov (2020)[6]	0	0	0	0	0	1	1	1	3	low
Gutierrez-Ortiz (2020) [7]	0	0	1	1	0	1	1	1	5	moderate
Helms (2020)[8]	1	1	1	1	1	1	1	0	7	fair
Lechien (2020)[9]	1	1	1	1	1	0	1	1	7	fair
Li (2020)[10]	1	1	1	1	1	1	1	1	8	high
Lu (2020) [11]	1	1	1	1	1	0	0	1	6	moderate
Mao (2020)[12]	1	1	1	1	1	1	1	1	8	high
Moein (2020)[13]	1	1	1	0	0	1	1	1	6	moderate
Moriguchi (2020)[14]	1	1	1*	1	0	1	1	1	7*	fair
Padroni (2020) [47]	0	0	1	1	0	1	1	1	5	moderate
Poyiadji (2020)[15]	0	0	1	1	0	1	1	1	5	moderate
Sedaghat (2020)[16]	0	1	0	0	0	1	1	1	4	low
Sharifi-Razavi (2020) [17]	0	0	0	1	0	0	1	1	3	low
Toscano (2020)[18]	1	1	1*	1	1	1	1	1	8*	high
Vollono (2020)[19]	0	0	0	1	0	1	1	1	4	low
Xiang (2020)[20]§	0	0	1*	1	0	1	0	0	3*	low
Yan (2020)[21]	1	0	1	0	1	0	1	1	5	moderate
Ye (2020)[22]	0	0	0	0	0	1	1	1	3	low
Yin (2020) [23]	0	0	0	1	0	1	1	0	3	low

Zhang (2020) [31]	0	0	0	1	0	1	1	1	4	low
Zhao (2020)[24]	0	1	0	0	0	1	1	1	4	low
Zhao (2020)[25]	0	0	0	1	0	0	1	1	3	low

*tested viral RNA in CSF

§untraceable

Table 1. Reports on neurologic disorders in association with respiratory SARS-CoV-2 infection

Author	Theme	Design	n	SARS-Cov-2 testing	Neurological assessment	CSF	Brain imaging	Other neurological workup	Main findings	Potential limitations
Bagheri (2020) [15]	smell	cross sectional	10069		no neurological assessment; smell loss evaluated with a self-reported online questionnaire	not performed	NA	NA	48.2% of patients reported anosmia/hyposmia	no neurological/diagnostic workup, no data on CSF
Beltrán-Corbellini (2020) [16]	smell/taste	case-control study	119	nasopharyngeal swab	no neurological assessment; smell and taste loss evaluated with a patient-completed questionnaire	not performed	NA	NA	39.2% of patients reported smell/taste dysfunction vs 12.5% of patients with influenza (controls)	no neurological/diagnostic workup, no data on CSF
Bernard-Valnet (2020) [28]	encephalitis	case series	2	nasopharyngeal swab (positive) CSF (negative)	case 1: NCSE, no meningism case 2: headache, mental status changes, focal signs, no meningism	negative viral RNA testing, high proteins	MRI: normal	EEG (case 1): anterior spike-and waves, irregular slow theta background	"encephalitic symptoms" in patients with SARS-COV-2	negative viral RNA testing on CSF, normal neuroimaging
Chen (2020) [10]	neurologic disease	retrospective case series	274	nasopharyngeal swab	no specific workup; data extracted from charts	not performed	NA	NA	hypoxic encephalopathy in 20% of deceased patients, occurrence in later disease stage; cerebrovascular disease in 1% of patients	no data on neurological assessment and workup
Duong (2020) [29]	encephalitis	case report	1	nasopharyngeal swab	headache, fever, seizure, meningism	high proteins 70 white cells	CT: normal	EEG: unspecific slowing	meningo-encephalitis due to SARS-CoV-2	no brain MRI, no CSF viral testing
Filatov (2020) [34]	encephalopathy	case report	1	unspecified	encephalopathy (patient nonverbal, unable to follow any commands, no motor/sensory deficit, no meningism)	normal glucose, normal protein, no cells, no viral RNA testing	CT: no acute lesions	EEG: bilateral slowing and focal slowing in the left temporal region with sharply countered waves	encephalopathy due to SARS-CoV-2 No abnormalities in CSF	no SARS-Cov-2 PCR in CSF
Gutierrez-Ortiz (2020) [21]	peripheral nervous system	case series	2	nasopharyngeal swab (positive) CSF (negative)	case 1: right internuclear ophtalmoparesis, ataxia case 2: multiple cranial neuropathies	negative viral RNA testing. case 1 had positive GD1b-IgG, case 2 not tested	NA	No	Miller-Fisher syndrome 5 days after COVID-19 onset; cranial neuropathies 3 days after COVID-19 onset	negative viral RNA testing on CSF; no brain imaging or nerve conduction studies

Helms (2020) [18]	neurologic disease	multicenter observational prospective	58	nasopharyngeal swab	65% of patients with COVID-19 related ARDS in ICU had confusion, 69% agitation, 67% pyramidal signs, 36% dysexecutive syndrome	n=7: elevated proteins (n=1), negative PCR for SARS-Cov-2 (n=7)	MRI (n=13): focal leptomeningeal enhancement (n=8), perfusion abnormalities (n=11), diffusion-weighted ischemic lesions (n=3)	EEG: unspecific changes	encephalopathy is common in patients with ARDS due to COVID-19; single acute DWI ischemic lesions can be seen on MRI.	all patients had negative viral RNA testing on CSF; only 8% assessed before sedation/neuromuscular blockade
Lechien (2020) [14]	smell/taste	Multicenter observational prospective	417	nasopharyngeal swab	no neurological assessment; smell and taste loss evaluated with a patient-completed questionnaire	not performed	No	no	85% of patients reported olfactory dysfunction, 88% gustatory dysfunction; both associated with fever	no neurological/diagnostic workup, no data on CSF
Li (2020) [12]	acute cerebrovascular disease	retrospective observational	221	nasopharyngeal swab	no specific workup; data extracted from charts	not performed	MRI consistent with cerebrovascular disease	no	5% of patients developed acute ischemic stroke, 0.5% cerebral venous sinus thrombosis, 0.5% cerebral hemorrhage	no neurological/diagnostic workup, no data on CSF
Lu (2020) [19]	seizure	multicenter retrospective	304	nasopharyngeal swab	8 (2.6%) encephalopathic; 2 had “seizure-like” presentation, diagnosed as acute stress reaction (1) and electrolyte disturbance (1)	not performed	NA	NA	no patient admitted with COVID-19 had a seizure or status epilepticus	no routine or continuous EEG performed
Mao (2020) [8]	neurologic disease	retrospective observational case series	216	nasopharyngeal swab	CNS manifestations (dizziness, headache, impaired consciousness, cerebrovascular disease, ataxia, seizure), peripheral nervous system (taste impairment, smell impairment, vision impairment, and nerve pain), and skeletal muscular injury manifestations were assessed	not performed	NA	NA	36.4% of COVID-19 patients had neurological manifestations, which were more prevalent in patients with more severe disease course	no neurological/diagnostic workup, no data on CSF
Moein (2020) [17]	smell	case-control study	120	nasopharyngeal swab	no neurological assessment; smell and taste loss evaluated with a objective validated test	not performed	NA	NA	85.0% of patients had moderate hyposmia to anosmia vs 0% of healthy controls	healthy controls picked from previous database; no data on brain imaging and CSF
Moriguchi (2020) [27]	encephalitis	case report	1	nasopharyngeal swab (negative)	coma (Glasgow Coma scale 6), neck stiffness, generalized	high opening pressure, colorless and clear, 12	MRI: peri-ventricular temporal DWI	no	SARS-Cov-2 can cause ventriculitis and encephalitis; viral RNA was	1/2 samples on CSF positive for viral RNA at first (re-

				CSF (positive)	seizures during transport and in later disease stage (treated with levetiracetam)	cells/microliter (10 mononuclear cells, 2 polymorphonuclear cells); RT-PCR positive for SARS-Cov-2 RNA	hyperintensity, hyperintense right mesial temporal and hippocampal region on FLAIR, no contrast enhancement		detected in CSF, brain MRI showed involvement of temporal lobe, patient presented generalized seizures (treatment included ceftriaxone, vancomycin, acyclovir, steroids, levetiracetam, favipinavir)	analysis showed 2/2 positive); Differential diagnosis with hippocampal sclerosis accompanying post-convulsive encephalopathy
Padroni (2020) [47]	peripheral nervous system	case report	1	nasopharyngeal swab	moderate symmetric distal limb weakness, loss of deep tendon reflexes, preserved sensation	high proteins (dissociations with no cellularity)	NA	Nerve conduction studies consistent with motor-sensory demyelinating polyneuropathy	GBS developed 22 days after first COVID-19 symptom	no viral RNA testing on CSF; no antiganglioside antibody testing
Poyiadji (2020) [26]	encephalitis	case report	1	nasopharyngeal swab	fever and altered mental status (no neurological examination reported)	negative bacterial culture, negative tests for HSV, Varicella-Zoster, West Nile virus; testing for the presence of SARS-CoV-2 in the CSF was unable to be performed	MRI: hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions	no	acute necrotizing encephalopathy associated with SARS-Cov-2 (treated with IVIG)	no viral RNA testing on CSF; necrotizing encephalopathy also attributable to cytokine storm (rather than SARS-CoV-2 direct neuroinvasion)
Sedaghat (2020) [48]	peripheral nervous system	case report	1	nasopharyngeal swab	acute progressive symmetric ascending quadriparesis	not performed	MRI (brain and cervical): normal	Nerve conduction studies consistent with motor-sensory axonal involvement	GBS (AMSAN) two weeks after COVID-19 infection	no data on CSF; hypothesized a post-infectious autoimmune sensitization (no supporting serology data)
Sharifi-Razavi (2020) [33]	stroke	case report	1	nasopharyngeal swab	headache, haemoptysis, confusion	not performed	CT: intracerebral hemorrhage	no	intracerebral hemorrhage associated with SARS-Cov-2	no data on CSF, no data on coagulation screening
Toscano (2020) [11]	peripheral nervous system	case series	5	nasoharyngeal swab (positive) CSF (negative)	flaccid areflexic tetraparesis (n=3), paraparesis (n=1), facial diplegia and limb paresthesia (n=1)	high proteins (dissociation with no cellularity) (n=3), normal proteins (n=2); negative antiganglioside antibodies (n=3/3), negative SARS-Cov-2	MRI (brain and cervical): enhancement of nerve roots or facial nerve (n=3/5)	Nerve conduction studies consistent with axonal variant (n=3) and demyelinating variant (n=2) of GBS	GBS developed 5 to 10 days after first symptoms of COVID-19; response to IVIG was poor in 2 cases. SARS-CoV-2 IgG positive in 3/5 patients.	no data on other potential pathogens, antiganglioside antibodies tested negative

						RNA (n=5/5)				
Vollono (2020) [49]	seizure	case report	1	nasoharyngeal swab	NCSE in a patient with post-HSV1 encephalitis structural epilepsy	not performed	MRI: temporo-parietal gliosis (previous encephalitis), no acute lesions	EEG: left centro-temporal lateralized semi-rhythmic delta activity	NCSE as sole manifestation of SARS-CoV-2	no data on CSF, NCSE attributable to structural epilepsy and fever
Xiang (2020) [25]§	encephalitis	case report	1	nasoharyngeal swab CSF (positive)	seizures and persistent hiccups developed 96 hours after starting mechanical ventilation; meningism, pyramidal signs	high opening pressure, colorless, clear, PCR positive for SARS-Cov-2 RNA	CT: normal	NA	Acute encephalitis associated with SARS-Cov-2 (treated with IVIG, steroids, antibiotics, antiseizure medications)	no brain MRI data, methods for PCR on CSF not available
Yan (2020) [13]	smell/taste	cross-sectional	262	nasopharyngeal swab	no neurological assessment; smell and taste loss assessed with a subjective olfaction test	not performed	no	no	Smell and taste loss in 68% and 71% of SARS-CoV-2 positive vs 16% and 17% in negative subjects	no data on CSF or brain imaging; only smell and taste tested; no consecutive enrollment; phone survey
Ye (2020) [22]	encephalitis	case report	1	nasopharyngeal swab (negative) CSF (negative)	meningism and pyramidal signs	normal opening pressure, normal biochemistry, RT-PCR negative for SARS-Cov-2 RNA, with IgM and IgG not detectable	CT: normal	no	presumed encephalitis associated with SARS-CoV-2 infection	no data on brain imaging, negative nasopharyngeal and CSF testing
Yin (2020) [23]	meningitis	case report	1	nasopharyngeal swab (negative) CSF (negative)	meningismus and pyramidal signs	normal opening pressure, high proteins, negative for SARS-Cov-2 RNA	CT: normal	no	presumed SARS-CoV-2 nervous system invasion through meninges	no advanced neuroimaging performed, negative viral RNA testing on CSF
Zhang (2020) [31]	ADEM	case report	1	nasopharyngeal swab	encephalopathy, dysphagia, dysarthria (ADEM)	normal, no viral RNA testing	MRI: atypical ADEM	no	atypical ADEM in a patient with SARS-CoV-2	no CSF viral testing, no spinal cord MRI, brain MRI atypical for ADEM
Zhao (2020) [20]	peripheral nervous system	case report	1	nasopharyngeal swab	symmetric weakness, areflexia, distal decrease of thermo-dolorific sensation	normal cell count, increased proteins; viral testing not performed	no	Nerve conduction studies: demyelinating neuropathy	GBS 8 days before COVID-19 onset	Swab test positive 8 days after onset of neuropathy No SARS-CoV-2 PCR on CSF No microbiological assessment at diagnosis
Zhao (2020) [30]	myelitis	case report	1	nasopharyngeal	flaccid paraparesis, urinary and	not performed	CT: no acute lesion	no	presumed SARS-CoV-2 myelitis	no data on spinal cord MRI, no

	swab	bowel incontinence, sensory thoracic level, decreased tendon reflexes		developing 7 days after fever onset	CSF analysis, 4/6 swabs negative

§ publication is untraceable in ChinaXiv; data extracted from hospital site report, available at http://www.bjdth.com/html/1/151/163/3665.html

Legend. ADEM: acute disseminated encephalomyelitis; AMSAN: acute motor-sensory axonal neuropathy; ARDS: acute respiratory distress syndrome; CNS central nervous system; COVID-19: coronavirus related disease; CSF: cerebrospinal fluid; CT: computerized tomography; DWI: diffusion-weighted imaging; FLAIR: fluid-attenuated inversion recovery; GBS: Guillain-Barré syndrome; EEG: electroencephalography; MRI: magnetic resonance imaging; NCSE: non-convulsive status epilepticus; PNS: peripheral nervous system; RNA: ribonucleic acid; NA: not available; RT-PCR: real-time polymerase chain reaction.

Table 2. Recommendations for reporting of clinical features, ancillary examination in patients with SARS-CoV-2 infection and nervous system involvement

General		current symptoms, medical history, comorbidities and concomitant medication
Clinical features and neurophysiological studies	focal neurological signs	findings of neurological examination
	central nervous system	acute/subacute, standardized definition of encephalopathy and encephalitis [16]
	peripheral nervous system	neurological examination, lab results with full myopathy panel, and nerve conduction studies/electromyography
	seizures	report semiology and seizure type according to ILAE guidelines [28]; EEG findings according to standardized reporting
Neuroimaging	head CT	report abnormal findings, brain edema, focal contrast enhancement, vascular status
	brain MRI	abnormal findings, focal parenchymal, leptomeningeal contrast enhancement or vasculitic changes
	spine MRI	abnormal findings, contrast-enhancement (including cranial nerves or peripheral nerve roots in cases of suspected acute neuropathy), myelopathy/atrophy
SARS-Cov-2 viral RNA testing	nasopharyngeal swab	results; if multiple test performed, report time point of positive results
	immunoassay	antibodies assay (IgM/IgG titers)
	CSF	results PCR (qualitative and quantitative, if available) and IgM/IgG antibodies in CSF and serum (intrathecal SARS-CoV-2-specific antibody production)
CSF analysis	routine analysis	opening pressure, erythrocyte and leukocyte count with differential, glucose, proteins, oligoclonal bands and IgG index
	differential for neuroinfections and autoimmune conditions	gram stain, bacterial culture, PCR testing for and common neurotropic viruses (HSV, VZV, enterovirus), cryptococcal antigen testing, venereal diseases testing (if suspected); further testing for following infectious agents according to medical history, immune status, age and travel history: CMV, Toxoplasma gondii, Mycobacterium tuberculosis, Treponema pallidum, Borrelia species, opportunistic fungal infections,

		tick-borne encephalitis virus, Toscana virus and West-Nile virus
Lab serum testing	routine studies	cell blood count and leukocyte differentials, D-Dimer, electroytes, LDH, C-reactive protein, kidney and liver function
	infectious and autoimmune disease	routine blood cultures, HIV serology, treponemal testing (if suspected), autoimmune antibodies
Treatment	antivirals, steroids/ immunomodulatory treatments, anticonvulsive medication, symptomatic therapy	specific drug type, dosage, route of administration
	outcome	short (7 days) and long-term outcome (3 to 6 months)

Legend. CMV: cytomegalovirus; CSF: cerebrospinal fluid; CT: computerized tomography; EEG: electroencephalography; HIV: human immunodeficiency virus; HSV: Herpes Simplex virus; ICU: intensive care unit; LDH: lactate dehydrogenase; MRI: magnetic resonance imaging; PCR: polymerase chain reaction; VZV: Varicella-zoster virus; ILAE International League Against Epilepsy